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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 05/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/721,391	VILE ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,15 and 34-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,15,34-43 and 45-67* is/are rejected.

7)☒ Claim(s) *44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5, 14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application has been transferred to a new examiner, Quang Nguyen, Ph.D. in the AU 1636.

Applicants' amendment filed on March 04, 2003 in Paper No. 15 has been entered.

Note that the amendment contains two newly added claims 42 (page 5). Per 35 CFR 1.126, new claims 34-66 have been renumbered as claims 34-67. To avoid any confusion in future Amendments, renumbered claims 34-67 should be used.

Accordingly, claims 9, 15 and 34-67 are pending in the present application, and they are examined on the merits herein.

Claim Objections

Claims 45 and 63 are objected to because of the following informalities: the term "activateable" is mispelled. Appropriate correction is required.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see page 13, line 1, page 15, line 4, for examples). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Upon furth r consid ration, following is a new ground of rejection.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 9, 15, 34-43 and 45-67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a composition comprising a nucleic acid, wherein the nucleic acid comprises: (a) a cell type-specific promoter, e.g. human Tyr300 (SEQ ID NO:1), for activating the expression of a gene in a specific cell type, (b) a therapeutic gene sequence operably linked to said cell type-specific promoter, (c) an amplification promoter element for amplifying transcription of said therapeutic gene in said specific cell type; and (d) a sequence encoding a transcription activator, said

transcription activator for activating said amplification promoter element, wherein said nucleic acid produces a level of mRNA expression which is at least 100-fold higher in *in vitro* cells of the specific cell type compared to *in vitro* cells which are not of the specific cell type. The claims encompass a composition comprising a nucleic acid containing any cell type-specific promoter, including human Tyr300 (SEQ ID NO:1), operably linked to any amplification promoter element and any sequence encoding any transcription factor that activates the amplification promoter element in any combination, so that the nucleic acid produces a level of mRNA expression which is at least 100-fold higher in *in vitro* cells of the specific cell type compared to *in vitro* cells which are not of the specific cell type. However, apart from the exemplification showing the highly tissue-specific heat shock element (HSE)-Tyr-300/heat shock factor–1 (HSF-1) feedback loop system that can be used to kill melanoma cells specifically and efficiently, the instant specification fails to teach a representative number of species of a nucleic acid comprising any cell-type specific promoter in combination with any amplification promoter element and any sequence encoding a transcription factor that activates the amplification promoter element, and said nucleic acid produces a level of mRNA expression which is at least 100-fold higher in *in vitro* cells of the specific cell type compared to *in vitro* cells which are not of the specific cell type. It has been known in the art that tissue-specific promoters are often either **very weak and/or leaky** (Sato et al., Biochem. Biophys. Res. Commun. 244:455-462, 1998, see page 455; Nettelbeck et al., TIG 16:174-181, 2000, see page 175, first full paragraph; Emiliusen et al., Gene therapy 8:987-998, 2001). Apart from the human Tyr300 (SEQ ID NO. 1) promoter

which is transcriptionally silent in all of the non-melanoma cells tested, the instant specification fails to teach any other tyrosine promoter element that also has the same promoter activity as that of Tyr300, let alone for any other cell-type specific promoter. Additionally, the instant specification fails to teach any other amplification promoter element and its corresponding encoded transcription activator to act in conjunction with the Tyr300 promoter to obtain the desired results as those obtained for the HSE-Tyr-300/HSF-1 feedback loop system. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot fully envision the detailed structure of a nucleic acid comprising any cell type-specific promoter in combination with any amplification promoter element and any sequence encoding a transcription activator that activates the amplification promoter as claimed apart from the disclosed HSE-Tyr-300/HSF-1 feedback loop nucleic acid system, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One

cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 9, 15, 34-43 and 45-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a nucleic acid, wherein said nucleic acid comprises: (a) a cell type-specific promoter of SEQ ID NO:1; (b) a therapeutic gene sequence operably linked to said cell type-specific promoter; (c) an amplification promoter element for amplifying transcription of said therapeutic gene in said therapeutic gene in said specific cell type; and (d) a sequence encoding a transcription activator for activating said amplification promoter element, wherein said amplification promoter element comprises at least an HSE and said transcriptional activator is HSF-1;

does not reasonably provide enablement for a composition comprising a nucleic acid, wherein said nucleic acid comprises any cell type-specific promoter, any amplification promoter element and any sequence encoding a transcription activator for activating said amplification promoter element. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The claims are drawn to a composition comprising a nucleic acid, wherein the nucleic acid comprises: (a) a cell type-specific promoter, including the human Tyr300 (SEQ ID NO:1), for activating the expression of a gene in a specific cell type, (b) a therapeutic gene sequence operably linked to said cell type-specific promoter, (c) an amplification promoter element for amplifying transcription of said therapeutic gene in said specific cell type; and (d) a sequence encoding a transcription activator, said transcription activator for activating said amplification promoter element, wherein said nucleic acid produces a level of mRNA expression which is at least 100-fold higher in *in vitro* cells of the specific cell type compared to *in vitro* cells which are not of the specific cell type.

The specification teaches by exemplification the highly tissue-specific heat shock element (HSE)-Tyr-300/heat shock factor–1 (HSF-1) feedback loop system that can be used to kill melanoma cells specifically and efficiently. The evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the following reasons.

(1) The breadth of the claims. The instant claims encompass a composition comprising a nucleic acid containing any cell type-specific promoter, including human Tyr300 (SEQ ID NO:1), operably linked to any amplification promoter element for amplifying transcription of a therapeutic gene sequence and any sequence encoding any transcription factor that activates the amplification promoter element (not necessarily limited to stress inducible promoter elements and stress inducible transcriptional activators) in any combination, so that the nucleic acid produces a level of mRNA expression which is at least 100-fold higher in *in vitro* cells of the specific cell type compared to *in vitro* cells which are not of the specific cell type.

(2) The state and unpredictability of the prior art. At about the effective filing date of the present application, Dang et al. (Clin. Cancer Res. 5:471-474, 1999) noted that further advancement in all fields such as gene delivery, gene expression and host immune manipulation is needed to make gene therapy a reality. Dang et al. particularly pointed out several factors limiting an effective gene therapy, including sub-optimal vectors, the lack of a stable *in vivo* transgene expression, the adverse host immunological responses to the delivered vectors and most importantly an efficient gene delivery to target tissues or cells (last paragraph, col. 2, page 474). Verma & Somia (Nature 389:239-242,1997) reviewed various vectors known in the art for use in gene therapy, and the problems that are associated with each. Verma & Somia also indicated that appropriate enhancer-promoter sequences can improve expression, but that the "search for such combinations is a case of trial and error for a given cell type." (page 240, sentence bridging columns 2 and 3). Nettelbeck et al. (TIG 16:174-181,

2000) indicated there is a need to improve or design promoters with the desired specificities for tumor targeting, and that additional layers of selectivity are required to construct highly efficient and specific vectors (see abstract and Outlook section).

(3) The amount of direction or guidance provided. Apart from the exemplification showing the highly tissue-specific heat shock element (HSE)-Tyr-300/heat shock factor–1 (HSF-1) feedback loop system that can be used to kill melanoma cells specifically and efficiently, the instant specification fails to teach any other nucleic acid comprising any cell-type specific promoter in combination with any amplification promoter element and any sequence encoding a transcription factor that activates the amplification promoter element, and wherein said nucleic acid produces a level of mRNA expression which is at least 100-fold higher in *in vitro* cells of the specific cell type compared to *in vitro* cells which are not of the specific cell type. Apart from the human Tyr300 (SEQ ID NO. 1) promoter which is transcriptionally silent in all of the non-melanoma cells tested, the instant specification fails to teach any other tyrosine promoter element that also has the same promoter activity as that of Tyr300, let alone for any other cell-type specific promoter. It is unclear which other cell-type specific promoters would possess the same promoter activity as that of human Tyr300, particularly it has been known in the art that tissue-specific promoters (e.g., albumin, PSA, MCK, GFAP, NSE) are often either **very weak and/or leaky**. Additionally, the instant specification fails to teach any other amplification promoter element and its corresponding encoded transcription activator to act in conjunction with the Tyr300 promoter to obtain the desired results as those obtained for the HSE-Tyr-300/HSF-1 feedback loop system. Although Applicants

mentioned cursory U.S. Patent Nos. 6,034,228; 5,827,685 and 5,770,581 in reference to other stress inducible promoter elements and stress inducible transcriptional activators (page 22, last paragraph), Examiner notes that the instant specification fails to teach any encoded transcriptional activator(s) to be utilized for activating the radiation responsive enhancer or amplification promoter element disclosed in U.S. Patent No. 5,770,581, or any amplification promoter element activated by the stress protector proteins taught by U.S. Patent No. 5,827,685, and that a human Ste20-like serine/threonine signal transduction kinase of U.S. Patent No. 6,034,228 has nothing related to the presently claimed invention. Therefore, given the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make the composition having the desired properties as claimed. Furthermore, with respect to the breadth of the instant claims, Applicants' attention is further directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Additionally, the courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues raised above, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 40 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 40 and 59, the phrase "the cytotoxic gene is GALVenv, HSVTK, cytosine deaminase, nitroreductase, or VSV-G glycoprotein" is unclear. How can any of GALVenv, HSVTK, cytosine deaminase, nitroreductase and VSV-G glycoprotein actually be a gene (made up of nucleotides)? The metes and bounds of the claims are not clearly determined. Examiner suggests the substitution of the term "is" with - - encodes - - to overcome this rejection.

Conclusions

No claims are allowed.

Claim 44 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to LIE, Zeta Adams, whose telephone number is (703) 305-3291.

Quang Nguyen, Ph.D.

Gerald G. Leffers Jr
PATENT EXAMINER
Gerald G. Leffers Jr
A.U. 1636